REMARKS

The Examiner has rejected claim 1 under 35 U.S.C. 102(e) in view of U.S. 6,361,942 ("Coull"). Claim 1 is directed to a method of analyzing a nucleic acid sample. It requires the addition of a probe which can hybridize to a target sequence if the target sequence is present in the sample. The probe has an internal tag sequence. If the target sequence is present, the probe hybridizes to the target and allows the generation of a derivative molecule that includes a strand in which the internal capture tag sequence is no longer internal but is at the end of the product. Presence of the target sequence can be evaluated by detecting the repositioning of the capture tag to a terminal position. For example, a terminal capture tag can be detected by hybridization and ligation to capture probes with capture tag-complementary single stranded overhangs. In the absence of a corresponding target sequence, the capture tag remains internal to the probe/primer molecule and, in this example, is not detected.

Coull does not describe or suggest generation of one or a plurality of derivative molecules in which the capture tag is repositioned from an internal region of a strand to one or both of its termini. One general description of Coull's method is at column 7, lines 38 to column 8, line 32:

> Detection Complexes . . . are hybrids of at least two component polymers. At least two of the component polymers of the Detection Complex comprise at least one moiety from a set of donor and acceptor moieties. . . . When the Detection Complex . . . is formed, at least one donor moiety of the component polymer is brought sufficiently close in space to at least one acceptor moiety of a second component polymer. Since the donor and acceptor moieties of the set of the assembled Detection Complex are closely situated in space, transfer of energy occurs between moieties of the set. When the Detection Complex dissociates, the donor and acceptor moieties do not interact sufficient to cause substantial transfer of energy. . . . The Detection Complexes . . . are primarily designed to dissociate as a direct or indirect consequence of hybridization of one or more segments of a component polymer to a target sequence of a target molecule. [emphasis added].

Thus, in Coull, if a target sequence is present, a Detection Complex can dissociate. However, dissociation of components of a nucleic acid hybrid differs from generation of a derivative molecule in which a capture tag is repositioned from an internal region to one or both termini.

The Examiner refers to Figures 20 and 21 of Coull on page 3 of the Office action. Those Figures teach an assay for the presence of polymerase using Coull's "Substrate Detection

Complexes." If polymerase is present, the terminus labeled 89 in Figure 20 A is extended, thereby displacing probe 86, and thereby separating (i.e., dissociating) the signalling pair B and A (numbered 80 and 81 in Figure 20A). There is no internal sequence tag which changes from a position internal to a strand to a position at an end of a strand.

However, the claimed invention requires that probe/primer having a capture tag sequence which is internal in a nucleic acid strand be converted to one which has the capture tag sequence at an end of the strand. This alteration in sequence position is not depicted in Figure 20 or anywhere else in Coull. FIG. 20 is described at column 30, line 43 to column 31, line 23 of Coull. Polymerase activity is detected by dissociation of the polymer 80 from the polymer 81:

> [T]he polymerase will read to the end of the annealing polymer 81 to thereby displace component polymer 80 and dissociate the Substrate Detection Complex [90]. [emphasis added].

(column 30, lines 62-65, Coull)

Similarly for FIG. 20B:

> [T]he polymerase will read to the end of the annealing polymer 92 to thereby displace component polymer 80 and dissociate the Substrate Detection Complex [91]. [emphasis added].

(column 31, lines 20-23, Coull)

The Examiner also cites FIG. 21. FIG. 21 is an elaboration of the embodiment depicted in FIG. 20. Again, there is no internal sequence tag which changes from a position internal to a strand to a position at an end of a strand. In FIG. 21=-, a target sequence 101 is detected using unlabeled probes 106 and 107 which are linked to an enzyme 102. The target sequence 101 is then detected indirectly by assaying for the activity of the enzyme 102 using dissociation of a "Substrate Detection Complex 90" as described for FIG. 20. FIG. 21 is described at column 31, lines 36-60 of Coull:

> With reference to FIG. 21, an embodiment of using a Substrate Detection Complex in a probe-based hybridization assay to detect a target molecule is illustrated. The probe/target complex (99) to be detected using the Substrate Detection Complex (90) is formed from the target molecule (100), having a target sequence 101 to which the unlabeled probes 106 and 107 hybridize. The enzyme labeled probe 103, comprising enzyme moiety (102) is then further complexed to arms of the unlabeled probes 106 and 107. . . . According to the illustration, the enzyme (102), then acts upon the Substrate Detection Complex (90; See FIG. 20) to thereby extend the terminus of the hairpin stem and form the duplex 108. Formation of the duplex 108 result in release of the component polymer 80 and dissociation of the Substrate Detection Complex. Upon dissociation,

there is a measurable change in detectable signal from at least one member of a Beacon Set which can be used to detect or identify the presence, absence or quantity of the target sequence or target molecule in the assay. [emphasis added].

Thus, neither FIG. 20 nor FIG. 21 describes generation of a derivative molecule in which a capture tag is repositioned from an internal region to one or both termini.

With respect to forming a reaction mixture in which one or a plurality of derivative molecules are generated if a target sequence and a corresponding probe/primer molecule are both present, the Examiner specifically cites column 18, line 20 to column 20, line 14 of Coull. This text is organized into sections, which are addressed, one by one, as follows:

1. Lines 21 to 50 of column 18 describe "Detectable and Independently Detectable Moieties/Multiplex Analysis" using "Detection Complexes." There is no teaching nor suggestion that a Detection Complex be used to generate one or a plurality of derivative molecules in which a capture tag is repositioned from an internal region to one or both termini.

2. Line 51 of column 18 to line 12 of column 19 describes "spacer/linker moieties." There is no teaching nor suggestion of generating one or a plurality of derivative molecules by repositioning a spacer or linker from an internal region to one or both termini of such molecules.

3. Lines 13 to 47 of column 19 describe "Hybridization Conditions/Stringency," for example, modulating stringency factors to control stringency of hybridization of the probing segment of a Detection Complex to a target sequence. Again, here, there is no teaching nor suggestion that a Detection Complex be used to generate one or a plurality of derivative molecules in which a capture tag is repositioned from an internal region to one or both termini.

4. Line 63 of column 19 to line 14 of column 20 describes "Blocking Probes," e.g., "probes which can be used to suppress the binding of a probing segment of the probing polymer to a non-target sequence." There is no teaching nor suggestion that a blocking probe be used to generate one or a plurality of derivative molecules in which a capture tag is repositioned from an internal region to one or both termini.

Because Coull's description of dissociation of a Detection Complex does not equate with nor suggest the repositioning of a capture tag from an internal position to a terminal position,

Applicant submits that the 102(e) rejection of claim 1 and claims dependent therefrom should be withdrawn.

The Examiner has rejected claim 42 under 35 U.S.C. 103, citing U.S. 6,361,942 ("Coull") in view of U.S. 6,261,797 ("Sorge"). The method of claim 42 includes cleaving probe molecules of a set of molecules for which a complementary sequence is present among nucleic acids in a sample. The cleavage positions a capture tag sequence at a terminus of the cleaved probe molecules. The cleaved probes are detected to analyze the sample.

Coull does not describe a probe molecule that includes an internal capture tag that is repositioned to a terminus by cleavage and does not suggest any use of cleavage to detect nucleic acid in a sample.

Sorge also does not describe a probe molecule that includes an internal capture tag that is repositioned to a terminus by cleavage. Sorge describes, for example, PCR amplifying a nucleic acid sequence using primers and cleaving the resulting PCR products for the purpose of cloning a particular nucleic acid. For example, at column 5, lines 16-25:

> When . . . primers are used to amplify a polynucleotide product, and then treated with type IIS restriction endonuclease, the polynucleotide sequences in the synthesis product which comprise the type IIS recognition sequence are completely or partially removed. Thus, using the methods of the invention, one may efficiently synthesize and manipulate polynucleotides of interest by primer mediated polynucleotide synthesis, e.g., PCR, without introducing some or all of the primer-derived nucleotides. . . .

Thus, Sorge suggests that primers used for sequence amplification be excised and discarded. Moreover, Sorge suggests that the cleavage occur in a region external to the primer so that the primer can be completely removed. Partial removal may result from cleavage in the annealing region (see, e.g., column 5, lines 47-50). However, Sorge does not teach or suggest a cleavage that causes includes an internal capture tag to be repositioned from an internal position to a terminus position to produce a cleaved probe that is detected. Because neither Coull nor Sorge teaches or suggests at least this feature of claim 42, Applicant submits that the obviousness rejection of claim 42 and claims dependent therefrom should be withdrawn.

Applicant does not concede any positions of the Examiner that are not expressly addressed above, nor does Applicant concede that there are not other good reasons for patentability of the presented claims or other claims.

Applicant asks that all claims be allowed.